REMARKS

Initially, Applicant's attorney wishes to thank Examiner Kim for the careful consideration given the present application. Applicant's attorney would also like to extend his thanks to both Examiner Kim and Examiner Criares for the courteous interview extended the undersigned on July 9, 2003. While both Examiner Criares and Kim suggested they would look favorably upon, and likely allow, claims which included a limitation directed to a "synergistic" combination of Hmg-CoA Reductase Inhibitors and L-arginine, Applicant does not believe the art nor case law requires such a limitation.

During the interview, three primary issues were addressed: (i) Applicant's position that no new matter was introduced by addition of the terms "atorvastatin" and "cerivastatin" into the claims; (ii) Applicant's position that, at the very least, the genus method claims were allowable and that only a bare genus composition claim would be impacted by the prior art;[1] and (iii) the inapplicability of the art rejections especially in light of the previously allowed composition claims and method claims. As will be discussed in detail below, both composition and method claims have already been issued to Applicant in U.S. Pat. No. 5,968,983 in Markush format, and method claims to the genus of Hmg-CoA Reductase Inhibitors have issued in Applicant's U.S. Pat. No. 6,465,516. Importantly, these cases were allowed over the same art as is currently cited by the Examiner.

For the Examiner's convenience, the following remarks are provided in discreet sections addressing each of these issues in the manner presented above and discussed during the interview.

I. New Matter Rejection under 35 U.S.C. § 112.

Initially, the Examiner objected to the amendment filed October 18, 1999, under 35 U.S.C.§132 because it purportedly introduced new matter into the disclosure. Similarly, claims 20, 21, 23-26 have been rejected under 35 U.S.C.§112 for failing to provide adequate written description due to the inclusion of atorvastatin and cerivastatin in these claims. The

[1] That is, interpretation of a composition claim to include only Hmg-CoA Reductase Inhibitor and L-arginine, ignoring the other words in the claim.

Examiner stated that these two species should be removed from the specification and cancelled from the claims because they purportedly introduce new matter. The new matter rejection, as the Examiner noted, may be properly labeled as a written description rejection under 35 U.S.C.§112, and thus will be addressed as such for purposes of these arguments. See MPEP § 2163.

It is respectfully submitted that the specification fully satisfies the written description requirement of 35 U.S.C.§112 and that Applicant is not introducing new matter. As previously addressed, Applicant's specification need not describe the claimed invention in *ipsis verbis* to comply with the written description requirement[2]. Relevant case law provides that an objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed."[3] The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter."[4] It is certainly not a requirement of *ipsis verbis* support.

In Ex Parte Sorenson,[5] (attached herein) for example, the Board addressed a written description issue very analogous to that raised in the present case. Specifically, the claims in Sorenson recited (1) "binuclear copper complexes of carboxylic acids", and (2) "a binuclear copper complex of an aliphatic carboxylic acid or binuclear copper complex of an aryl carboxylic acid". The specification supported the broad expressions "an organic compound of copper", "copper complexes of carboxylic acids", the "copper complex of an aliphatic carboxylic acid", and the "copper complex of an aryl carboxylic action". The Examiner in Sorenson

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[2] In re Edwards, 568 F.2d 1349, 196 USPQ 465 (CCPA 1978).

[3] In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed.

[4] Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)).

[5] 3 U.S.P.Q.2d 1462 (CCPA 1987)

initially rejected the claim expressions at issue, stating that the claimed compounds "do not appear in the original disclosure", meaning that he do not find literal support therein. The rejection was reversed on appeal. The Board was persuaded that the Specification contained adequate written description to satisfy §112. The specification presented five examples of binuclear copper complexes of carboxylic acids. The Board concluded that the examples together with the broader disclosure of copper complexes of carboxylic acids, both aliphatic and aromatic, was undoubtedly adequate disclosure to reasonably convey that appellant had possession of the subject matter claimed.

As in Sorenson, the present disclosure recites a broad expression of a family of compounds, "the family of those substances known as Hmg-CoA Reductase Inhibitors." As in Sorenson, the present Specification also recites various examples of the member compounds of that family. As in Sorenson, the specific list of the inhibitors of Hmg-CoA Reductase were "by way of example" and were therefore used to demonstrate that the inventor had possession of the invention. As in Sorenson, the presently claimed compounds were not explicitly delineated in the Specification, but are supported nonetheless. As the Board in Sorenson found support for the claimed "binuclear copper complexes of carboxylic acids" based on a disclosure of "an organic compound of copper", the specific inhibitors of atorvastatin and cerivastatin are implicitly and inherently supported in the application as originally filed.

Similarly, the Board reaffirmed its test of sufficient written description in another more recent chemical case,[6]. In Union Oil Co. (attached herein), the description recited ranges of chemical properties which work in combination with ranges of other chemical properties to produce an automotive gasoline. The Board found an adequate written description under §112 even though the exact chemical components of each combination were not disclosed and the specification did not disclose any distinct embodiments corresponding to any claim at issue.

It is respectfully submitted that the Applicant have meet the written description requirement under 35 U.S.C.§112. The Specification recites, "L-arginine may be used in

[6] Union Oil Co. of California v. Atlantic Richfield Co., 208 F.3d 989, 54 USPQ2d 1227, 1232-22 (Fed. Cir. 2000),

conjunction with virtually any of the family of those substances known as Hmg-CoA Reductase Inhibitors" (page 9, lines 13-14). Additionally, the Specification states (page 1, lines 9-18),

> Much focus in the area of cardiac disease has been on the presence of cholesterol in the body. ... It is known that 50% or more of the total body cholesterol in humans is derived from intrinsic biosynthesis. It is also known that a rate-limiting step of major significance in the biosynthesis of cholesterol is at the level of the enzyme known as 3-hydroxy-3-methylglutaryl-coenzyme A reductase or Hmg-CoA reductase. A general class of compounds is known in the art which inhibit and reduce the intrinsic biosynthesis of cholesterol in order to reduce the risk factor of hypercholesterolemia and coronary artery death. This general class of compounds is known as inhibitors of Hmg-CoA reductase.

Therefore, the Applicant has demonstrated possession of the "family of those substances known as Hmg-CoA Reductase Inhibitors," as evidenced by this disclosure. One of ordinary skill in the art would understand that any substance known as a Hmg-CoA Reductase Inhibitor would satisfy the present invention. One skilled in the art would have been familiar with the family of Hmg-CoA Reductase Inhibitors, including atorvastatin and cerivastatin. Both inhibitors, atorvastatin and cerivastatin, are undisputedly within the "family of those substances known as Hmg-CoA Reductase Inhibitors."

Both inhibitors, atorvastatin and cerivastatin, were also known in the art, at the time the priority application was filed. U.S. Patent No. 5,447,922, issued September 5, 1995, and U.S. Patent No. 5,543,542, issued August 6, 1996 identified similar Hmg-CoA Reductase Inhibitors. Both of these Patents issued well before the priority date of April 10, 1997. Atorvastatin (also known as Lipitor™) was approved by the FDA on December 16, 1996 and cerivastatin was approved by the FDA on June 3, 1997. Clearly, both of these compounds were well known at the priority date.

As the Examiner is aware, Applicant is not required to disclose every compound that could logically fit into a category of compounds. The task would be overly burdensome; both for the Applicant and for the Examiner to read and review such a description. A labeling of a group of compounds with a sufficient description that is known in the art, such as Hmg-CoA

Reductase Inhibitors, is sufficient support for all such members of a definite family of compounds.

Applicant respectfully submit that the Claims 20, 21, 23-26 do not contain new matter because the disclosure in the Specification of the parent Application is sufficient to demonstrate possession of the invention. Therefore, the Applicant requests that these claims be given the priority date of their parent application, Application No. 08/833,842, now U.S. No. Patent 5,968,983.

II. Claim Rejection under 35 U.S.C. § 102(e).

This issue of "new matter" impacts the art rejections made by the Examiner under 35 U.S.C.§102(e). If the limitations discussed above are given proper priority the Liao et al reference is not prior art under 35 U.S.C.§102(e).

However, if the Examiner maintains the new matter rejection, Applicant reserves the right to address the Liao reference with a Rule 1.131 Affidavit. Such an Affidavit would be successful in overcoming the Liao reference because it is clear that Applicant's original disclosure predates the filing date of U.S. Patent No. 6,147,109 to Liao. An Affidavit under Rule 131 would simply reiterate that which is clearly stated in the application, namely that the disclosure of Hmg-CoA Reductase Inhibitors and the recitation of "L-arginine being used in "conjunction with virtually any of the family of those substances known as Hmg-CoA Reductase Inhibitors" (page 9, lines 13-14) clearly supports an earlier filing date than Liao. This statement in affidavit form would remove the Liao reference from being cited against the present application as cerivastatin and atorvastatin were known Hmg-CoA Reductase Inhibitors. If an Affidavit is necessary, in the event the Examiner insists on the new matter rejection, Applicant's attorney would appreciate if the Examiner would state what she considers critical to the Affidavit.

III. Claim Rejection under 35 U.S.C. § 103.

Before addressing each of the Examiner's specific rejections, it must be pointed out that each and every piece of art has been previously addressed and overcome in Applicant's related applications. In support of this, Applicant's attorney references the composition and

method claims from the '983 Patent (limited to a Markush recitation). Also, a representative independent method claim of U.S. Pat. No. 6,465,516, which recites the genus of Hmg-CoA Reductase Inhibitors, is provided below in its entirety. The Applicant asks the Examiner to note that claim 1 of '516 does not contain the present limitation of L-argrinine as provided in the current pending claims.

> 1. A method for treating a subject who would benefit from increased Nitric Oxide production in a tissue comprising:
> administering to the subject in need of such treatment, irrespective of the subject's cholesterol level, a Hmg-CoA Reductase Inhibitor in an amount effective to increase Nitric Oxide production in said tissue of the subject. (emphasis added)

Turning to the art cited by the Examiner, Claims 1, 2, 5, 6, 12, 13, 16 and 17 have been rejected under 35 U.S.C.§103(a) as being obvious over Morris et al.(1994). It is respectfully submitted that this reference has been previously addressed in the parent application and been found to not anticipate nor make obvious claims of similar scope to those being presented herein. In particular, Morris' teaching of a single Hmg-CoA Reductase Inhibitor arginine salt, without any suggestion, motivation or otherwise rationale for using it to treat a disease state in no way anticipates or makes obvious the present invention. Initially, the Examiner is directed to the fact that claims 1, 2, 5, 6 and 16 and 17 are method claims and that all of the limitations recited therein (i.e. "treating a disease") should be read into the claim. Additionally, the preamble of therapeutic composition claims 12 and 13 breaths life and meaning into these claims, and therefore Morris does not even impact claims 12 and 13. Accordingly, the rejection should be withdrawn.

Claims 1-6, 12, 13, 16-19 and 22 stand rejected under 35 U.S.C.§103(a) as being unpatentable over U.S. Patent No. 5,634,895 to McGovern et al. and U.S. Patent No. 5,634,895 to Igo et al. The Examiner seems to be repeating the objection previously presented and addressed in the parent application. As the Examiner points out, the claims do differ in claiming combinations of L-arginine and Hmg-CoA Reductase Inhibitors. The Examiner also states,

however, that it "would have been obvious because all of the components are well known individually for treating restenosis following angioplasty".

To rebut Applicant's previously submitted arguments regarding McGovern and Igo, the Examiner states that "regardless of the purposes of the mechanism of the action of each of the active agents, . . . the ultimate effect is the same." This statement is inconsistent with the Examiner's burden of establishing a prima facie case of obviousness and the case cited. The case law only supports a prima facie case of obviousness when a combination of elements were known for the same purpose. The Examiner has shown no suggestion of motivation to combine the elements, and no reasonable expectation of success. The Examiner's reliance on this case law is misplaced. To the extent that the case law applies, it requires that the two elements have the same purpose, not the same end result as stated by the Examiner.

As was pointed out previously, L-arginine and pravastatin as described in McGovern and Igo are not used for the same purpose and the idea of combining them would not flow logically from their individual teachings. The Examiner further states, with regard to claims 16 and 17 that a method of stimulating NO acting agents involves a mechanism of action which is inherent in the treatment of medical disease conditions. It is respectfully pointed out to the Examiner that any use of inherency is limited by the recognized utility of the agent by the prior art. The utility of these two agents was not recognized. As is clearly as is demonstrated by the numerous patents that have been issued to Applicant and others in this field, the utility that has been described and claimed by Applicant was not known in the prior art.

Only through Applicant's teaching is one motivated to administer both L-arginine and an agent that enhances NO production (e.g., via enhanced conversion of L-arginine into NO). The Federal Circuit has consistently held that in order to establish a proper prima facie case of obviousness, the PTO must show a motivation apart from the teaching of the invention to combine the references. Since neither reference suggests or teaches a reason for the combination of either agent with the other, it is respectfully submitted that a prima facie case of obviousness

has not been established.[7] There is no suggestion in McGovern that there would be any benefit or advantage gained by combining a Hmg-CoA Reductase Inhibitor and L-arginine. Nor is there any suggestion or teaching in Igo that L-arginine would provide any added benefit to a Hmg-CoA Reductase Inhibitor formulation. Accordingly, the rejection should be withdrawn.

The Examiner also rejected claims 2, 5, 6 and 19 under 35 U.S.C.§103(a) as being obvious since they are within the knowledge of the skilled pharmacologist and conventional routes of administration. While Applicant's attorney does not agree with the Examiner's position on these claims, these dependent claims should be allowed based upon their dependency on the claims presented above that are in condition for allowance.

Finally, the Examiner has rejected claims 1, 2, 5, 12, 13, 20, 21 and 24-26 under 35 U.S.C.§103(a) for being obvious over Wang et al. (1994), Pharmacol. Res. (1996) and U.S. Patent No. 6,093,719 to Bocan. The stated basis for the obviousness rejection of claims provided in the Office Action is that Wang purportedly teaches that dietary L-arginine prevents atherogenesis in the coronary artery of the hypercholesterolemic rabbits. The Examiner states that the Pharmacol. Res. reference teaches that cerivistatin interferes with a major process involved in atherogenesis and Bocan teaches that atorvastatin alone results in a less atherogenic lipoprotein profile. In the opinion of the Examiner, "combinations of L-arginine and cerivistatin or atorvastatin to treat a condition such as atherogenesis would have been obvious because all of the components are well known individually for treating atherogenesis." Applicant respectfully disagrees for the reasons discussed above.

As presented in the arguments above, it is respectfully asserted that the purpose provided in the art of administering a Hmg-CoA Reductase Inhibitor (i.e., atorvastatin) is to reduce serum cholesterol to thereby reduce platlet aggregation (see e.g., column 2, lines 46-51 of Bocan), and the purpose of administering L-arginine is to form NO thereby reducing vasoconstriction (see e.g., abstract of Wang). Accordingly, even assuming arguendo that cerivistatin, atorvastatin, and L-arginine are described in the art as set forth by the Examiner,

[7] The Federal Circuit, in, *In re Rouffe* reversed an obviousness rejection where, as in this case, the Examiner improperly pieced together elements in the prior art when there was not motivation to do so. 47 USPQ2d 1453, 1457-1458 (Fed. Cir. 1998).

these teachings do not satisfy a prima facie case of obviousness. The two claimed elements (e.g., L-arginine and cerivistatin / atorvastatin) are not used for the same purpose, and the idea of combining them would not flow logically from the individual teachings.

Furthermore, neither Wang nor Bocan provides any motivation to combine L-arginine and a Hmg-CoA Reductase Inhibitor. Absent such motivation or suggestion, it is improper to combine the references in support of an obviousness rejection under 35 U.S.C.§103. See the discussion above. Bocan is directed towards a method of treatment of atherosclerosis, which will restore endogenous vascular endothelium-dependent activities. Again, Bocan fails to recognize any role that an Hmg-CoA Reductase Inhibitor plays in activation of NOS to result in vasodilation.

CONCLUSION

In conclusion, it is respectfully requested that the Examiner pass this case to issue. In view of the remarks presented above, it is believed that pending claims 1-6, 12, 13 and 16-22 are in condition for allowance and notice to such effect is respectfully requested. Should the Examiner have any questions regarding the above, the Examiner is invited to contact the undersigned at her convenience.

Respectfully submitted,

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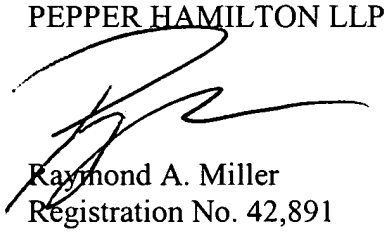

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